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DATA EVALUATION RECORD - SUPPLEMENT
for original review see TXR. 013953

STUDY TYPE: Reproduction and Fertility Effects Study – Rat [OPPTS 870.3800 (§83-4) OECD 416].

PC CODE: 098701 **DP BARCODE:** D313630

TEST MATERIAL (PURITY): 97 ± 1%

SYNONYMS: Methyl 3-(3-methylcarbaniloyloxy) carbanilate; 3-methoxycarbonylaminophenyl 3-methylcarbanilate

CITATION: McAnulty, P. (2000) Two-generation Reproduction Toxicity Study with Phenmedipham T.O.P. techn. Sample in Rats (3rd addendum to MRID No. 44862702; Company No. C98701). Scantox DK, 4623 Lille, Skensved Denmark. Study No. 10600. December 12, 2000. MRID 45316801. Unpublished.

Kallesan, T. (1986) Phenmedipham: Two Generation Reproduction Toxicity Study with Phenmedipham T.O.P. Technical Sample in Rats: Lab Project Number: A10600: 62908. Unpublished study prepared by Scantox Biologist Laboratorium. 146 p. MRID 44862702 {OPPTS 870.3800}

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REVISED EXECUTIVE SUMMARY: The minor revisions to this Executive Summary (R. Hawks, 11/29/99), including the reclassification of the study from **unacceptable** to **acceptable,** are based on the data provided in the supplemental report.

In a 2-generation reproduction toxicity study (MRID 44862702) Phenmedipham (97 ± 1% a.i.) was administered continuously in the diet to Wistar rats (24/sex/dose) at dose levels of 0, 25, 75 or 225 mg/kg/day (achieved 0, 24.8/25.1, 73.1/77.5 or 211.5/242.4 mg/kg/day in the P animals and 0, 26.3/28.1, 81.4/87.6 or 249.4/268.1 mg/kg/day in F_1 animals [M/F], respectively). Exposure to P animals began at approximately 6 weeks of age and lasted for 10 weeks prior to mating. F_1 pups selected (24/sex/dose) to produce the F_2 generation were exposed to the same dosage as their parents on postnatal day (PND) 21 and continuously throughout the rest of the study. F_1 animals were administered the test article for 10 weeks prior to mating to produce the F_2

animals. Mating to produce a second F_{2b} generation was not performed. Exposure of all animals to the test material was continuous throughout the study.

When compared to concurrent controls, there was no evidence of treatment-related changes in mortality, reproductive performance, gross pathology, histopathology or clinical signs observed in the P or F_1 animals. There were no changes of toxicological concern in food consumption. When compared to concurrent controls, differences in body weight of toxicological concern occurred in high-dose F_1 females throughout the premating period (↓9-15%) and on lactation day (LD21) (↓13%) and in high-dose F_1 males from premating day 0 through 35 (↓7-13%)($p \leq 0.05$). In the high-dose P dams, body weight gain (↓14%) and food efficiency (↓16%) were non-significantly decreased during the premating period.

No changes of toxicological concern were observed in the low-or mid-dose males and females.

No treatment-related differences in mortality were observed at any time in the F_1 and F_2 litters. No significant treatment-related clinical or behavioral abnormalities were seen in the offspring from treated groups.

When compared to concurent controls, decreases ($p \leq 0.05$) in body weight were observed in the mid-dose F_2 female pups on postnatal days (PNDs) 7, 14 and 21 (↓8-11%). Body weight gain, as calculated by the reviewers for the lactation period (PNDs 1-21), was reduced in the mid-dose F_2 male (↓10%) and female pups (↓12%). High-dose F_1 male and female pups displayed decreased ($p \leq 0.05$) body weight on PNDs 14 and/or 21 (↓7-10% vs. controls); body weight was decreased in high-dose F_2 male and female pups (↓15-19%) ($p \leq 0.05$) on PNDs 14 and 21. Body weight gain for PNDs 1-21 was reduced in the high-dose F_1 male (↓10%) and female pups (↓11%) and in the high-dose F_2 male (↓22%) and female pups (↓20%). Decreases in pup body weight are suggestive of an effect on lactation and are considered a reproductive effect, however, body weight decreases at PND 14 and above may result from a combination of decreased lactation and ingestion of test compound in the diet.

No changes of toxicological concern were observed in the low-dose pups.

The LOAEL for parental toxicity is 225 mg/kg/day in male and female rats (achieved dosages of 211.5/242.4 [M/F]) based on decreased body weight in males and decreased body weight, body weight gain and food efficiency in the females. The NOAEL is 75 mg/kg/day (achieved dosages of 73.1/77.5 [M/F]).

The LOAEL for reproductive/offspring toxicity is 75 mg/kg/day (achieved dosages of 81.4/87.6 [M/F]) based on decreased pup body weight and body weight gain. The NOAEL is 25 mg/kg/day (achieved dosages of 26.3/28.1 [M/F]).

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproduction toxicity study (OPPTS 870.3800; OECD 416) in the rat.

COMMENTS: This is a revised Executive Summary only and does not alter the conclusions of the previous review with regard to **NOAELS** and **LOAELs.**

The original classification of this study was **Unacceptable/Guideline** but upgradeable because data for P dam gestation weight, adult and pup clinical signs and gross pathology for pups were not included in the study report.

1.) P dam gestation weight: The current submission includes summarized and individual data for gestation and lactation weights in P and F_1 dams. The means and standard deviations for the individual data were verified by the reviewer and did not always concur with those values presented in the DER, as indicated in Table 1. However, since the differences between the values in the supplemental report and the DER are relatively small, they do not affect the conclusions in the DER.

TABLE 1. Body weight gain (g) during gestation (days 0-20) and body weight (g) on day 21 of lactation for P and F_1 dams.

Dose group (mg/kg/day)			
0	25	75	225
GESTATION BODY WEIGHT GAIN			
P Dams[1]			
78.6 ± 27.1[a]	76.3 ± 33.1	85.0 ± 23.2	73.1 ± 26.1
F_1 Dams[1]			
93.9 ± 22.3	101.0 ± 13.4	95.5 ± 14.6	89.3 ± 21.6
LACTATION BODY WEIGHT			
P Dams[1]			
268.9 ± 16.1	263.3 ± 22.7	262.2 ± 17.9	243.7 ± 19.1
F_1 Dams[2]			
267.3 ± 12.5	253.4 ± 21.0	251.8 ± 15.8	231.3 ± 17.8

[a] Presented values are means ± SD; data from pages 15-18 of the supplemental report.
[1] Values do not concur with those in the DER.
[2] Values concur with those in the DER.

2.) Adult and pup clinical signs: These data, which were included in the supplemental report, do not show any significant treatment-related effects.

3.) Gross pathology of pups: The supplemental report stated that "the original study protocol stated that necropsy of offspring after weaning would only be performed on animals that had shown clinical or behavioral abnormalities (OECD guideline number 416). As no such treatment-related abnormalities occurred, no post-weaning necropsies were performed".

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.